

## **Clinical investigations of medical devices**

### **1. Purpose of this information sheet**

This information sheet provides details regarding requirements for clinical investigations of medical devices. It is particularly intended for sponsors of clinical investigations, clinical investigators and members of Ethics Committees.

It should be noted that the information contained may not be complete. The legal texts and standards should be consulted on a case-by-case basis. Clinical trials of medicinal products are the subject of separate information.

### **2. Overview of the requirements for clinical investigations**

For investigations of medical devices, Swiss legislation on therapeutic products bases its provisions on the European Medical Devices Directives 90/385/EEC and 93/42/EEC and the harmonised European standards EN ISO 14155-1 und -2 on the clinical investigation of medical devices for human subjects. The national requirements are defined in the Federal Law on Medicinal Products and Medical Devices (Heilmittelgesetz, HMG, SR 812.21) and in the Ordinance on Clinical Trials of Therapeutic Products (VKlin, SR 812.214.2).

These requirements suppose that the medical device to be investigated is ready for the intended use for human subjects, that the investigation plan fulfils basic scientific and ethical criteria, and that precautionary measures intended to protect the subjects' health are in place. The standards also describe the fundamental obligations on the part of the sponsors and the clinical investigators, monitoring, and the content of important documents (investigation plan with case report forms (CRFs), investigator's brochure, final report).

#### **a) Compliance with the standards EN ISO 14155-1 and -2**

*VKlin Art.4, Art.9, letter j*

Compliance with the standards EN ISO 14155-1 and -2 is a legal requirement in Switzerland. Deviations are possible but must be presented to the Ethics Committees in a transparent way and require their explicit approval.

The revised standard ISO 14155:2011 was published in February 2011 and can be applied with immediate effect.

#### **b) Informed consent by the investigation subjects**

*HMG Arts.54, 55, 56; VKlin Art.6 para.2*

The HMG describes the fundamental requirements relating to obtaining the informed consent of the investigation subjects and also to clinical investigations in special situations (minors, persons under judicial disability or persons incapable of judgment, emergency situations). In addition, No. 4.8 of the ICH GCP guideline must be respected in Switzerland for all trials of therapeutic products (see [www.ich.org](http://www.ich.org) under Guidelines – Efficacy Topics).

### c) Coverage for harm caused

HMG Art.54 para. 1;  
VKlin Art.7, Art.9 letter I, Art.10 letter I

Clinical investigations may only be carried out if it is guaranteed that the investigation subjects will be fully compensated for any kind of harm caused.

The sponsor is primarily responsible for the said compensation. The sponsor can have recourse to other persons – for example the investigators – if they could also be liable. Dividing the loss among various persons and firms is possible and must be stated in the form of a contract. Restricting liability towards the investigation subjects is however not permitted, e.g. by a restriction clause in the patient consent form.

The Ethics Committees examine the information for the patients, and the guarantee of capacity to pay compensation in the case of harm, for every investigation. An insurance policy for clinical investigations is an appropriate guarantee. Other solutions such as earmarked funds, bank guarantees, etc., are rarely selected but are nevertheless permitted in principle. The Ethics Committee decides, on a case-to-case basis, whether the guarantee is appropriate and the funds to cover the harm are sufficient.

A separate information sheet describes insurance for clinical investigations and the information to be provided to the subjects regarding coverage in case of harm (see document "[Requirements for insurance policies for clinical trials on therapeutic products involving human subjects](#)")

It must be possible for subjects to claim damages in Switzerland. If the sponsor's registered offices are abroad, he must designate a company or an individual in Switzerland (guarantor) who is responsible for assuring payments. Examples of guarantors are a Swiss distributor, a Swiss Clinical Research Organisation (CRO), the clinical investigator, or a Swiss insurance company. The guarantor must be stated in the insurance policy. The investigation subjects must be informed of the name and address of the guarantor.

### d) Mandate and structure of the Ethics Committees

HMG Arts.54 and 57; VKlin Arts.9-10, Arts.29-34

The fundamental mandate and structure of the Ethics Committees were aligned throughout Switzerland by legislation on therapeutic products, and are stated in the above-mentioned articles of the HMG and VKlin.

### e) Notifications and approval

HMG Arts.54 und 57; VKlin Arts.9-10, 13, 14, 29-34, sections 6.-8.

#### 1. Mandatory notification: general aspects

Applications must be submitted to the Ethics Committees for **all** clinical investigations of medical devices.

Corresponding notifications must be submitted to Swissmedic for the following clinical investigations:

- Investigations with non-conforming medical devices (products without CE marking)
- Investigations with CE-marked medical devices, if the said devices are:
  - a) CE marked devices used outside the intended use(s) covered by the CE marking, e.g. other apparatus settings, indications, type of application, patient groups, or
  - b) may not be marketed in Switzerland for their intended use, e.g. when restrictions or bans are imposed.

The clinical investigator is in principle responsible for contacts with the Ethics Committee and the sponsor for contacts with Swissmedic.

The minimum documentation for first submissions regarding intended investigations is described in Arts. 9 and 14 of VKlin. Full documentation must be submitted with each application, and its contents must correspond to requirements described in the Medicinal Devices Directives 93/42/EEC and 90/385/EEC as well as the standards EN ISO 14155-1 and -2:2009 (the more recent standard ISO 14155:2011 may also be used).

Notifications of intended trials should be submitted to Ethics Committees using the "*Basic form for submitting a biomedical research project*" ([www.swissethics.ch](http://www.swissethics.ch), in the section "Templates"). Notifications to Swissmedic

also require completing the "*Notification form - Clinical trials with medical devices*" [www.swissmedic.ch/md.asp](http://www.swissmedic.ch/md.asp) (select "Regulatory aspects:...").

Modifications during the course of an investigation can be submitted without using a special format. Significant modifications must be approved by the Ethics Committee and evaluated by Swissmedic before they may be implemented.

Notification of the end of a clinical investigation must be submitted within 90 days, and a premature halt to an investigation within 15 days. In the case of a premature halt, reasons must be given and any consequences for the subjects must be stated. A final report must be submitted to Swissmedic within the six months following the end or the premature halt to an investigation.

## 2. Notifications regarding safety

a) Swissmedic and the Ethic Committee must be informed within two days of new circumstances that occur during the clinical investigation that can affect the safety of the subjects and of measures to protect the subjects (Art. 20 VKlin). Examples are newly discovered product deficiencies that could lead to serious events, new findings regarding risks, preventive and corrective measures (including those agreed upon by authorities or Ethics Committees abroad or required by them). To do so, please use the form "*Clinical investigations of medical devices: Notification of serious adverse events concerning Switzerland*". The sponsor and the investigators immediately take all necessary safety measures to protect the investigation subjects from immediate danger.

b) Serious incidents caused by medical devices that are authorised for the market and used according to their CE marking (e.g. post-market investigations):

Cases from Switzerland must be reported to Swissmedic, in accordance with Art. 15 of the Medical Devices Ordinance (MepV), using the forms for Vigilance. The web page [www.swissmedic.ch/marktueberwachung/00170/00275/index.html?lang=en](http://www.swissmedic.ch/marktueberwachung/00170/00275/index.html?lang=en) provides information on this subject. Cases from abroad must be reported to the relevant foreign competent authorities.

c) Serious adverse events in pre-market investigations that could have been caused by an investigational medical device<sup>1</sup> or in connection with a procedure<sup>2</sup> carried out during the clinical investigation (for the definition, see Appendix 1):

Such events must be reported within 7 days to the Ethics Committees and Swissmedic in accordance with Art. 24, VKlin. Expected events are not excluded from mandatory reporting, e.g. for clinical investigations with stents, stent thrombosis must be reported even if described in the protocol. For multi-national investigations, other types of events may also have to be reported to foreign authorities.

The following documents must be submitted:

- If the incident has taken place in Switzerland, use the form "*Clinical investigations of medical devices: Notification of serious adverse events concerning Switzerland*"
- For multi-centre trials, the updated tabular format in accordance with the guideline [MEDDEV 2.7/3](#). This Excel table is completed on a cumulative basis during the course of the investigation (with events worldwide). New events are always added at the beginning of the list, and all changes in comparison with the previous version are marked in colour or in bold. If necessary, Swissmedic may request additional information, notably in the case of unexpected adverse events and device deficiencies.

## 3. Reports on the safety of investigation subjects:

A report must be submitted spontaneously on a yearly basis, in accordance with Art. 24, VKlin (content see Appendix 2). If necessary, the Agency may also request more frequent information in accordance with Art. 27 VKlin.

---

<sup>1</sup> Investigational medical devices are not those that have been granted market authorisation or CE marked devices used outside the intended use(s) covered by the CE marking

<sup>2</sup> Interventions are medical or surgical procedures in connection with the use of the investigation product, and all interventions foreseen in the investigation plan that do not constitute routine treatment of the patient.

#### 4. Radiological protection

For the import and use of medical devices with ionising radiation, a permit must be obtained from the Swiss Federal Office for Public Health (BAG, Radiological Protection Division, CH-3003 Bern).

#### **f) Processing times**

*VKlin Arts.11 and 15*

Ethics Committees and Swissmedic process applications relative to clinical investigations of medical devices within a time limit of 30 days. This time limit begins on reception of the full documentation. The time limit may be extended if additional information must be obtained.

#### **g) Fees**

*HGebV Appendix 3, section 3 and Art. 4 Abs 1*

Ethics Committees charge fees depending on their individual rules.

The fees payable to Swissmedic are stipulated in the HGebV (Therapeutic Products Fees Ordinance). For notifications of pre-market investigations, Swissmedic charges CHF 1,000.-. Additional resources deployed for shortcomings or modifications are invoiced at an hourly rate of CHF 200.-.

#### **h) Data retention**

*VKlin Arts.25 and 33*

Generally speaking, a minimum retention period of 10 years is prescribed; for implants, the duration is 15 years.

#### **i) Surveillance**

*HMG Arts.54 and 57; VKlin Arts.12, 27-28, 33*

Ethics Committees assess every intended investigation as a routine procedure, and follow all ongoing investigations on the territory for which they are responsible. In the case of problems, they may withdraw their endorsement and thus halt an investigation. The Cantons are responsible for the supervision of the Ethics Committees.

Cantonal authorities can take action against physicians and health institutions within the framework of their health policing tasks. This can also, on a case-by-case basis, have an impact on a clinical investigation.

Swissmedic has a mandate and competence as the central control and co-ordination authority. It works in close collaboration with the Cantonal authorities and Ethics Committees, and may carry out inspections throughout Switzerland or examine documentation. In the case of irregularities and dangers, Swissmedic may initiate appropriate measures on a countrywide basis and inform the Swiss and foreign authorities thereof.

#### **j) Databanks and EUDAMED CIV ID**

*HMG Art. 64; Directive 2010/227/EU; Declaration of Helsinki Version 2008 (§ 19); Directive 2007/47/EC*

The EU and EFTA states maintain a databank (EUDAMED) which allows the identification of multinational clinical investigations and the co-ordination among the national regulatory authorities for medical devices in Europe. EUDAMED contains basic data on pre-market clinical investigations of medical devices and any

changes and national measures. As of 1 May 2011, every new pre-market clinical investigation will be given a EUDAMED CIV ID. The number is attributed by the first national authority to process a clinical investigation within Europe and is communicated to the sponsor. If a EUDAMED CIV ID has already been attributed, the sponsor should inform the other regulatory authorities concerned accordingly.

The EUDAMED databank is not public. This means that a EUDAMED CIV ID is not a substitute for listing in public registries (e.g. in [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Listing in a public registry is required by the Declaration of Helsinki. It is handled by the sponsor of the investigation prior to the recruitment of the first subject.

## **k) Penal provisions**

*HMG Arts.86-90*

The penal provisions in the event of offences or infringements are defined in the Law on Therapeutic Products. Penal proceedings within the Confederation's area of enforcement are led by Swissmedic.

### Contact

Swissmedic, Swiss Agency for Therapeutic Products  
Medical Devices division  
Hallerstrasse 7  
P.O. Box  
CH-3000 Bern 9  
Tel. +41 31 323 22 51 / Fax +41 31 322 76 46  
E-mail: [clinicaltrials.devices@swissmedic.ch](mailto:clinicaltrials.devices@swissmedic.ch)

Further information by Swissmedic on medical devices is available at [www.swissmedic.ch/md.asp](http://www.swissmedic.ch/md.asp).

### **Appendix 1: Definition of "serious adverse event"**

In accordance with VKlin, a serious adverse event is an incident that causes, or could have caused, the following:

- a) Death
- b) The following types of serious deterioration in the health of the subject
  - 1) Life-threatening illness or injury,
  - 2) Permanent impairment of a body structure or a body function,
  - 3) Hospitalisation or prolongation of hospitalisation,
  - 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent harm to a body structure or a body function,
- c) Foetal distress, foetal death or a congenital abnormality or birth defect.

Serious adverse events also include device deficiencies that could have led to a serious adverse event, if a) the measures taken had not been initiated or b) an intervention had not taken place or c) the circumstances could have led to a less fortunate outcome. Such situations must be reported as serious adverse events.

The following events are not considered to be serious: a planned stay in hospital as a result of pre-existing health problems, a procedure foreseen in the investigation plan and that is not carried out as a result of severe harm to health.

### **Appendix 2: Content of reports relating to the safety of investigation subjects**

The following information is of interest:

- Recruitment status, current number of study subjects worldwide and in Switzerland, current duration of follow-up;
- Expected serious adverse events (overview and discussion, including figures / frequency in the investigation arm, control arm and from scientific literature);
- Unexpected serious adverse events that could have been caused by the investigational medical device or by procedures carried out during the clinical investigation, device deficiencies (overview and discussion, including discussion of possible causes);
- Safety-relevant problems relating to the use of the medical devices at the investigation centres;
- Summary of safety measures taken or planned (by the sponsor, the Ethics Committees, the authorities);
- Findings in other clinical trials of the investigational device (if any);
- The sponsor's conclusion regarding the safety of the study subjects;
- Annexes, e.g. a listing of reportable SAE's to date.